Clinical trial results:
A phase I/II, open-label, study of intracerebral administration of adeno-associated viral vector containing the human alpha-N-acetylglucosaminidase cDNA in children with Sanfilippo type B syndrome

Summary

EudraCT number	2012-000856-33
Trial protocol	FR
Global end of trial date	27 November 2019

Results information

Result version number	v1 (current)
This version publication date	12 December 2020
First version publication date	12 December 2020

Trial information

Trial identification

Sponsor protocol code	AMT110-CD-001

Additional study identifiers

ISRCTN number	ISRCTN19853672
ClinicalTrials.gov id (NCT number)	NCT03300453
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	uniQure biopharma B.V
Sponsor organisation address	Paasheuvelweg 25A, Amsterdam, Netherlands, 1105BP
Public contact	Elise Destree, Elise Destree, +31 20 240 6000, E.Destree@uniqure.com
Scientific contact	Elise Destree, Elise Destree, +31 20 240 6000, E.Destree@uniqure.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2019
Global end of trial reached?	Yes
Global end of trial date	27 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical, radiological, biological tolerance associated to the proposed treatment

Protection of trial subjects:

Appropriate inclusion and exclusion criteria were applied.
An IDMC was appointed to
- be informed on the research protocol, informed consent documents and data safety reporting plans and monitoring plan;
- review the study performance and safety data and make recommendation(s) to the Sponsor on further study conduct, including:
o inclusion of the next patient in the protocol depending on clinical evolution of the already/previously treated subjects at 1 month after the immediate previous one,
o continuation of the trial,
o termination of the trial,
o modification to the trial;
by assessing the study progress, safety data and especially SUSARs.

Background therapy:

The following immunosupressive/anti-inflammatory agents were used:
- Modigraf (tacrolimus) - starting at 10 - 15 ng/mL, reducing progressively over the course of the study.
- Cellcept (mycophenolate mofetil) - 1200 mg/m2 for 2 weeks pre-surgery and 6 weeks post surgery.
- Prednisolone - 1mg/kg - for 10 days, starting on the day of surgery.

Evidence for comparator:

n/a

Actual start date of recruitment	17 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	66 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	3
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study began on 17 September 2013 and 4 patients were enrolled on the study.

Pre-assignment

Screening details:

Patients were screened against the eligibility criteria.
As the study consisted of a first in human trial, the patient recruitment was sequential.

Period 1

Period 1 title	Initial Phase (Until M12)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

n/a

Arms

Arm title	Human NAGLU gene - initial

Arm description:

Patients received a one-time treatment with human NAGLU gene

Arm type	Experimental
Investigational medicinal product name	rAAV2/5-hNaGlu
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intracerebral use

Dosage and administration details:

Administration of the investigational product (solution for injection) into the brain parenchyma and cerebellum at 8 image-guided tracks (6 cortical white matter, 2 cerebellum), with 2 deposits per track at different depths, in a single neurosurgical session. Each patient received 960 µL of vector suspension at 16 simultaneous vector deposit each containing 2.4x1011 vg (4x1012 vg in total) on Day 0 (study initial phase).

Number of subjects in period 1	Human NAGLU gene - initial
Started	4
Completed	4

Period 2	
Period 2 title	Extension Phase 1 (M12 to M30)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Blinding implementation details: n/a	

Arms	
Arm title	Extension Phase 1
Arm description: Follow up -Extension Phase 1	
Arm type	Follow Up
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Extension Phase 1
Started	4
Completed	4

Period 3	
Period 3 title	Extension Phase 2 (M30 to M66)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Blinding implementation details: n/a	

Arms	
Arm title	Extension Phase 2
Arm description: Follow-up - Extension Phase 2	
Arm type	Follow Up
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Extension Phase 2
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Human NAGLU gene - initial
Reporting group description:	
Patients received a one-time treatment with human NAGLU gene	

Reporting group values	Human NAGLU gene - initial	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	3	3	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Not specified	4	4	

End points

End points reporting groups

Reporting group title	Human NAGLU gene - initial
Reporting group description:	
Patients received a one-time treatment with human NAGLU gene	
Reporting group title	Extension Phase 1
Reporting group description:	
Follow up -Extension Phase 1	
Reporting group title	Extension Phase 2
Reporting group description:	
Follow-up - Extension Phase 2	

Primary: Adverse Events

End point title	Adverse Events[1]
End point description:	
All AEs identified in the period	
End point type	Primary
End point timeframe:	
As specified by the period	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical tests were performed. All patients received the same treatment. The primary objective was to look at safety.

End point values	Human NAGLU gene - initial	Extension Phase 1	Extension Phase 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: Number of events	63	60	32	

Statistical analyses

No statistical analyses for this end point

Primary: Serious Adverse Events

End point title	Serious Adverse Events[2]
End point description:	
End point type	Primary
End point timeframe:	
As specified by the period	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical tests were performed. All patients received the same treatment. The primary objective was to look at safety.

End point values	Human NAGLU gene - initial	Extension Phase 1	Extension Phase 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: Number of SAEs	1	6	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed throughout study

Adverse event reporting additional description:

Adverse events were assessed throughout the study. They data was collected in 3 time periods:
- Initial Phase (Until M12)
- Extension Phase 1 (M12 to M30)
- Extension Phase 2 (M30 to M66)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Initial Phase

Reporting group description:

Adverse events collected in the Initial Phase 1

Reporting group title	Extension Period 1

Reporting group description:

Adverse events collected in Extension Phase 1 (M12 to M30)

Reporting group title	Extension Period 2

Reporting group description:

Adverse events collected in Extension Phase 2 (M30 to M66)

Serious adverse events	Initial Phase	Extension Period 1	Extension Period 2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	3 / 4 (75.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasal polyps			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Transaminases increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia adenoviral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Escherichia pyelonephritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance	Additional description: Hydroelectolytic disorders linked to the bacterial infection		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Initial Phase	Extension Period 1	Extension Period 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Adenoidectomy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Ear tube insertion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 4 (75.00%)	3 / 4 (75.00%)	2 / 4 (50.00%)
occurrences (all)	5	7	2
Gait disturbance			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hyperthermia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Inflammation			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinitis			
subjects affected / exposed	4 / 4 (100.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	9	1	2
Bronchitis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	1	3	4
Bronchitis chronic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cough			

subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Sleep disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Investigations			
Carbon dioxide decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Haematocrit decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Protein total decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Red blood cell count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Alanine aminotransferase increased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Epstein-Barr virus test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Carbon dioxide increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Immunosuppressant drug level increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Magnetic resonance imaging brain abnormal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Varicella virus test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vitamin D decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Mitral valve incompetence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Cerebellar atrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cerebral haemosiderin deposition			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Presyncope			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Iron deficiency anaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Splenomegaly			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Otitis media			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	3	3	1
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	1	4	1
Tonsillectomy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)	3 / 4 (75.00%)	2 / 4 (50.00%)
occurrences (all)	6	6	2
Vomiting			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypertransaminasaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	3 / 4 (75.00%)
occurrences (all)	0	3	3
Gastroenteritis viral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Infectious mononucleosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Otitis externa			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Viral infection			

subjects affected / exposed	3 / 4 (75.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Lung disorder	Additional description: Lung infection		
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Varicella			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2013	Amendment 1: At the request of HCB and transmitted by the ANSM during the clinical and pharmaceutical evaluation of the AEC file, it was asked to specify the procedures for the transfer of the material (catheters) under a PSMII for purging.
22 May 2014	Amendment 2: In order to follow up on the 4 patients included in the clinical trial, the period of observation and follow-up of the safety of the test treatment is prolonged until 30 months post-surgery with the continuation of the treatment. immunosuppressive therapy (tacrolimus Modigraf®). This will track the progress of patients' health status and collect additional safety data and samples to meet protocol objectives.
07 January 2016	Amendment 3: 1) Change of the Promoter of the study. The Institut Pasteur transfers the legal and operational responsibility of this trial to a Dutch biotech company, uniQure biopharma B.V. (Tafelbergweg 51, 1105 BD Amsterdam, the Netherlands). 2) Extension of follow-up of 4 patients included in the 36-month clinical trial. Version 5 of protocol consisted in extending the follow-up of the 4 patients to 18 months post-surgery. With this second phase of extension, the total follow-up of the children will be 5 years, in accordance with the recommendations of the European Medicines Agency on the follow-up of patients administered with a gene therapy (EMEA / CHMP / GTWP / 60436 / 2007). It should be noted that during this second phase of extension, the dose of tacrolimus will continue to be reduced and potentially stopped from month 48 post-surgery, depending on the results of available immunological data. 3) Addition of serologies to Cytomegalovirus (CMV) and Varicella-Zoster Virus (VZV) at visits V23-M12 and V41-M30 when previous serologies are negative (note that these serologies are performed by the center at the same time as the Epstein-Barr virus serology (EBV), the results will be retrospectively collected for the V23-M12 visit that has already been performed for the 4 patients included). 4) Addition of a blood sample (volume = 3 ml) at visit V41-M30 for the analysis of total and neutralizing antibodies against transgene 5) Clarification that any adverse event spontaneously reported by the patient / parents, observed by the investigator as well as any laboratory or radiological abnormalities that occurred during the extension phase should be documented in the CRF and added a section describing the monitoring and reporting of adverse events qualified for special notification (in agreement with EMEA / CHMP / GTWP / 60436/2007)
09 January 2018	Amendment 4: The purpose of the amendment is to incorporate the tacrolimus tapering and discontinuation plan into the current protocol. This includes addition of a new Appendix which outlines the process, as well as adaptation of the protocol itself to include a new M51 (V48) sample and associated updates. In addition, administrative updates related to personnel and address changes were made, as well as correction of some typographical errors identified in the previous version.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported